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L4: Entry 1 of 18

File: USPT

Oct 15, 2002

DOCUMENT-IDENTIFIER: US 6464986 B1

TITLE: Method for treating pain by peripheral administration of a neurotoxin

Brief Summary Text (80):

"Targeting moiety" means a molecule that has a specific binding affinity for a cell surface receptor. The targeting moiety is not a Clostridial neurotoxin H.sub.C, or peptides derived from H.sub.c with at least one of its amino acid deleted, modified or replaced. The targeting moiety is a molecule which is not a Clostridial neurotoxin, for example can be a bradykinin.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw Desc
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☐ 2. Document ID: US 6461617 B1

L4: Entry 2 of 18

File: USPT

Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6461617 B1

TITLE: Recombinant toxin fragments

Brief Summary Text (5):

The clostridia neurotoxins share a common architecture of a catalytic L-chain (LC, ca 50 kDa) disulphide linked to a receptor binding and translocating H-chain (HC, ca 100 kDa). The HC polypeptide is considered to comprise all or part of two distinct functional domains. The carboxy-terminal half of the HC (ca 50 kDa), termed the H.sub.C domain, is involved in the high affinity, neurospecific binding of the neurotoxin to cell surface receptors on the target neuron, whilst the amino-terminal half, termed the H.sub.N domain (ca 50 kDa), is considered to mediate the translocation of at least some portion of the neurotoxin across cellular

membranes such that the functional activity of the LC is expressed within the target cell. The H.sub.N domain also has the property, under conditions of low pH, of forming ion-permeable channels in lipid membranes, this may in some manner relate to its translocation function.

Brief Summary Text (9):

(B) Clostridial Neurotoxin Heavy Chain H.sub.N Domain: a portion of the heavy chain which enables translocation of that portion of the neurotoxin molecule such that a functional expression of light chain activity occurs within a target cell. the domain responsible for translocation of the endopeptidase activity, following binding of neurotoxin to its specific cell surface receptor via the binding domain, into the target cell. the domain responsible for formation of ion-permeable pores in lipid membranes under conditions of low pH. the domain responsible for increasing the solubility of the entire polypeptide compared to the solubility of light chain alone.

Brief Summary Text (10):

(C) Clostridial Neurotoxin Heavy Chain H.sub.C Domain. a portion of the heavy chain which is responsible for binding of the native holotoxin to cell surface receptor(s) involved in the intoxicating action of clostridial toxin prior to internalisation of the toxin into the cell.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw Desc
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☐ 3. Document ID: US 6444209 B1

L4: Entry 3 of 18

File: USPT

Sep 3, 2002

DOCUMENT-IDENTIFIER: US 6444209 B1

TITLE: Hybrid botulin neurotoxins

Brief Summary Text (26):

In a separate embodiment of the method, hybrid genes contain the translocation domain of the heavy chain from one serotype, receptor binding domain of the heavy chain from another serotype, combined with the light chain of a third C. botulinum serotype. Thus, it is possible to construct a variety of new toxin molecules by combining any of the three functional domains from any C. botulinum neurotoxin serotypes.

Detailed Description Text (19):

In one embodiment, one may manipulate the neurotoxin gene sequences to combine functional domains from different serotypes in a novel gene. For example, the gene segment coding the catalytic light chain of a type A neurotoxin, the gene segment coding the channel forming domain of a type B neurotoxin and the gene segment coding the receptor-binding domain of a type E neurotoxin may be joined together by genetic engineering techniques, and hybrid neurotoxin expressed in the recombinant microorganism.

Detailed Description Text (64):

Using recombinant DNA technology, it is also possible to construct hybrid toxins containing not only the light

chain from one *C. botulinum* serotype and the heavy chain from another, but also hybrid genes which contain the translocation domain of the heavy chain from one serotype, receptor binding domain of the heavy chain from another serotype, combined with the light chain of a third *C. botulinum* serotype. Thus, it is possible to construct a variety of new toxin molecules by combining any of the three functional domains from any *C. botulinum* neurotoxin serotypes.

#### Detailed Description Text (68):

Several laboratories have cloned different clostridial neurotoxins genes or gene domains. *C. tetanus* neurotoxin (TeNT) receptor binding domain (about 1.4 kbp) has been expressed in *E. coli* (Fairweather, N. F., et al., *J. Bacteriol.* 165:21-27, 1986; Fairweather, N. F., et al., *FEBS Lett.* 323:218-222, 1993; Makoff, A. J., et al., *Biotechnology* 7:1043-1046, 1989a; Figueiredo, D., et al., *Inf. Immun.* 63:3218-3221, 1995), *Saccharomyces cerevisiae* (Romanos, M. A., et al., *Nucl. Acids Res.* 19:1461-1467, 1991) *Pichia pastoris* (Clare, J. J., et al., *Biotechnology* 7:455-460, 1991) *Lactococcus lactis* (Wells, J. M., et al., *Mol. Microbiol.* 8:1156-1162, 1993) and a baculovirus system (Charles, I. G., et al., *Inf. Immun.* 59:1627-1632, 1991). BoNT/A receptor binding domain (about 1.3 kbp) has been expressed in *E. coli* as well (Clayton, M. C., et al., *Inf. Immunol.* 63:2738-2742, 1995; Middlebrook, J. L. and Brown, J. E., *Curr. Top. Microbiol. Immun.* 195:89-122, 1995).

#### Detailed Description Text (80):

The subfragments of the BoNT/A gene encoding the entire light chain (nucleotides 1-1344), the entire heavy chain (nucleotides 1345-3891), channel forming (nucleotides 1345-2687) and receptor binding (nucleotides 2581-3891) domains or their truncated fragments (nucleotides 1345-1789; 1345-2083; 1345-2416; 3301-3891) of the heavy chain were cloned. This was accomplished via the polymerase chain reaction using specific oligonucleotides and *C. botulinum* chromosomal DNA as a template.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Draw Desc
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## ☐ 4. Document ID: US 6372226 B2

L4: Entry 4 of 18

File: USPT

Apr 16, 2002

DOCUMENT-IDENTIFIER: US 6372226 B2

TITLE: Intraspinal botulinum toxin for treating pain

#### Detailed Description Text (18):

As set forth above, we have discovered that a surprisingly effective and long lasting treatment of pain can be achieved by intraspinal administration of a neurotoxin to an afflicted patient. In its most preferred embodiment, the present invention is practiced by intrathecal injection of botulinum toxin type A. Significantly, we have discovered that dramatic, long term analgesic and/or improved patient function effects can be achieved through intraspinal administration of a neurotoxin by the methods disclosed herein even though the neurotoxin has not had attached or fused to it, by various manipulative techniques or technologies, a neuronal targeting moiety, such as a non-neurotoxin protein, to provide targeting specificity of the

neurotoxin for one or more particular types of neurons. Thus, the present invention excludes from its scope the use of any neurotoxins with one or more artificially attached or fused neuronal targeting moieties. A neurotoxin can display a natural binding affinity for a neuron (i.e. for a particular receptor on the surface of the neuron) due to the presence of a binding moiety inherent to the structure of the native neurotoxin molecule (for example, the binding domain of the heavy chain of a botulinum toxin, i.e. the H.sub.c fragment). Thus, for clarity "targeting moiety" or "neuronal targeting moiety" as used herein means a targeting moiety which provides to a neurotoxin specific or enhanced neuronal binding affinity and which is not a natural or inherent feature of the neurotoxin which has such a targeting moiety. Contrarily, "binding moiety" as used herein means the inherent component or domain of the native neurotoxin which provides neuronal binding affinity.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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## ☐ 5. Document ID: US 6333037 B1

L4: Entry 5 of 18

File: USPT

Dec 25, 2001

DOCUMENT-IDENTIFIER: US 6333037 B1

TITLE: Methods for treating pain with a modified neurotoxin

### Detailed Description Text (18):

As set forth above, we have discovered that a surprisingly effective and long lasting treatment of pain can be achieved by intraspinal administration of a neurotoxin to an afflicted patient. In its most preferred embodiment, the present invention is practiced by intrathecal injection of botulinum toxin type A. Significantly, we have discovered that dramatic, long term analgesic and/or improved patient function effects can be achieved through intraspinal administration of a neurotoxin by the methods disclosed herein even though the neurotoxin has not had attached or fused to it, by various manipulative techniques or technologies, a neuronal targeting moiety, such as a non-neurotoxin protein, to provide targeting specificity of the neurotoxin for one or more particular types of neurons. Thus, the present invention excludes from its scope the use of any neurotoxins with one or more artificially attached or fused neuronal targeting moieties. A neurotoxin can display a natural binding affinity for a neuron (i.e. for a particular receptor on the surface of the neuron) due to the presence of a binding moiety inherent to the structure of the native neurotoxin molecule (for example, the binding domain of the heavy chain of a botulinum toxin, i.e. the H.sub.c fragment). Thus, for clarity "targeting moiety" or "neuronal targeting moiety" as used herein means a targeting moiety which provides to a neurotoxin specific or enhanced neuronal binding affinity and which is not a natural or inherent feature of the neurotoxin which has such a targeting moiety. Contrarily, "binding moiety" as used herein means the inherent component or domain of the native neurotoxin which provides neuronal binding affinity.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 6. Document ID: US 6312708 B1

L4: Entry 6 of 18

File: USPT

Nov 6, 2001

DOCUMENT-IDENTIFIER: US 6312708 B1

TITLE: Botulinum toxin implant

Brief Summary Text (67):

The tetanus toxin bears many similarities to the botulinum toxins. Thus, both the tetanus toxin and the botulinum toxins are polypeptides made by closely related species of Clostridium (Clostridium tetani and Clostridium botulinum, respectively). Additionally, both the tetanus toxin and the botulinum toxins are dichain proteins composed of a light chain (molecular weight about 50 kD) covalently bound by a single disulfide bond to a heavy chain (molecular weight about 100 kD). Hence, the molecular weight of tetanus toxin and of each of the seven botulinum toxins (non-complexed) is about 150 kD. Furthermore, for both the tetanus toxin and the botulinum toxins, the light chain bears the domain which exhibits intracellular biological (protease) activity, while the heavy chain comprises the receptor binding (immunogenic) and cell membrane translocational domains.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 7. Document ID: US 6268159 B1

L4: Entry 7 of 18

File: USPT

Jul 31, 2001

DOCUMENT-IDENTIFIER: US 6268159 B1

TITLE: Imaging of colorectal cancer using ST receptor binding compounds

Brief Summary Text (97):

Toxins are useful as active moieties. When a toxin is conjugated to an ST receptor binding moiety, the conjugated composition is specifically delivered to a metastasized colorectal cell by way of the ST receptor binding moiety and the toxin moiety kills the cell. Toxins are generally complex toxic products of various organisms including bacteria, plants, etc. Examples of toxins include but are not limited to: ricin, ricin A chain (ricin toxin), Pseudomonas exotoxin (PE), diphtheria toxin (DT), Clostridium perfringens phospholipase C (PLC), bovine pancreatic ribonuclease (BPR), pokeweed antiviral protein (PAP), abrin, abrin A chain (abrin toxin), cobra venom factor (CVF), gelonin (GEL), saporin (SAP), modeccin, viscumin and volkensin. As discussed above, when protein toxins are employed with ST receptor binding peptides, conjugated compositions may be produced using recombinant DNA techniques. Briefly, a recombinant DNA molecule can be constructed which encodes

both the ST receptor ligand and the toxin on a chimeric gene. When the chimeric gene is expressed, a fusion protein is produced which includes an ST receptor binding moiety and an active moiety. Protein toxins are also useful to form conjugated compounds with ST receptor binding peptides through non-peptidyl bonds.

#### Brief Summary Text (126):

One aspect of the present invention relates to a method of treating individuals suspected of suffering from metastasized colorectal cancer. Such individuals may be treated by administering to the individual a pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is a peptide. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ

ID NO:54 and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a radiostable conjugated compound described in Example 1. The individual being treated may be diagnosed as having metastasized colorectal cancer or may be diagnosed as having localized colorectal cancer and may undergo the treatment proactively in the event that there is some metastasis as yet undetected. The pharmaceutical composition contains a therapeutically effective amount of the conjugated composition. A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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## ☐ 8. Document ID: US 6235289 B1

L4: Entry 8 of 18

File: USPT

May 22, 2001

DOCUMENT-IDENTIFIER: US 6235289 B1

TITLE: Intraspinal methods for treating pain

### Drawing Description Text (27):

As set forth above, we have discovered that a surprisingly effective and long lasting treatment of pain can be achieved by intraspinal administration of a neurotoxin to an afflicted patient. In its most preferred embodiment, the present invention is practiced by intrathecal injection of botulinum toxin type A. Significantly, we have discovered that dramatic, long term analgesic and/or improved patient function effects can be achieved through intraspinal administration of a neurotoxin by the methods disclosed herein even though the neurotoxin has not had attached or fused to it, by various manipulative techniques or technologies, a neuronal targeting moiety, such as a non-neurotoxin protein, to provide targeting specificity of the neurotoxin for one or more particular types of neurons. Thus, the present invention excludes from its scope the use of any neurotoxins with one or more artificially attached or fused neuronal targeting moieties. A neurotoxin can display a natural binding affinity for a neuron (i.e. for a particular receptor on the surface of the neuron) due to the presence of a binding moiety inherent to the structure of the native neurotoxin molecule (for example, the binding domain of the heavy chain of a botulinum toxin, i.e. the H<sub>sup</sub>C fragment). Thus, for clarity "targeting moiety" or "neuronal targeting moiety" as used herein means a targeting moiety which provides to a neurotoxin specific or enhanced neuronal binding affinity and which is not a natural or inherent feature of the neurotoxin which has such a targeting moiety. Contrarily, "binding moiety" as used herein means the inherent component or domain of the native neurotoxin which provides neuronal binding affinity.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 9. Document ID: US 6203794 B1

L4: Entry 9 of 18

File: USPT

Mar 20, 2001

DOCUMENT-IDENTIFIER: US 6203794 B1

TITLE: Modification of clostridial toxins for use as transport proteins

Brief Summary Text (4):

Tetanus toxin (TeTx) and botulinum toxin (BoNT) are potent neurotoxins that induce paralysis by mechanisms that involve the inhibition of neurotransmitter release. These Clostridial neurotoxins are initially produced as single-chain proteins of .about.150 kDa. Proteolytic cleavage then generates an active dichain molecule having a .about.100 kDa heavy (H) and a .about.50 kDa light (L) chain that are linked by a single interchain disulfide bond. The H chain contains domains which contribute to the binding of the toxin to neuronal cell surface receptors and which facilitate translocation of the L chain into cells. The L chain is responsible for blocking neurotransmitter release.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC	Draw Desc
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☐ 10. Document ID: US 6187536 B1

L4: Entry 10 of 18

File: USPT

Feb 13, 2001

DOCUMENT-IDENTIFIER: US 6187536 B1

TITLE: Methods of identifying and detecting pancreatic cancer

Brief Summary Text (82):

One aspect of the present invention relates to a method of treating individuals who have pancreatic cancer. Such individuals may be treated by administering to the individual a pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises a CCK A receptor specific binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises a CCK A receptor specific binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the CCK A receptor specific binding moiety is an antibody. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises a CCK A receptor specific binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the CCK A receptor specific binding moiety. The CCK A receptor binding moiety



may be a monoclonal antibodies, humanized antibodies, chimeric antibodies, primatized antibodies as well as humanized Fab fragments, humanized F(Ab)<sub>2</sub> fragments, chimeric Fab fragments, chimeric F(Ab)<sub>2</sub> Primatized fragments Fab fragments, primatized F(Ab)<sub>2</sub> fragments. In some embodiments of the present invention, the CCK A receptor specific binding moiety is asperlicin or L-364,718/MK-329. In some embodiments of the present, the active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC	Draw Desc
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## □ 11. Document ID: US 6113915 A

L4: Entry 11 of 18

File: USPT

Sep 5, 2000

DOCUMENT-IDENTIFIER: US 6113915 A

TITLE: Methods for treating pain

### Detailed Description Text (19):

As set forth above, we have discovered that a surprisingly effective and long lasting treatment of pain can be achieved by intraspinal administration of a neurotoxin to an afflicted patient. In its most preferred embodiment, the present invention is practiced by intrathecal injection of botulinum toxin type A. Significantly, we have discovered that dramatic, long term analgesic and/or improved patient function effects can be achieved through intraspinal administration of a neurotoxin by the methods disclosed herein even though the neurotoxin has not had attached or fused to it, by various manipulative techniques or technologies, a neuronal targeting moiety, such as a non-neurotoxin protein, to provide targeting specificity of the neurotoxin for one or more particular types of neurons. Thus, the present invention excludes from its scope the use of any neurotoxins with one or more artificially attached or fused neuronal targeting moieties. A neurotoxin can display a natural binding affinity for a neuron (i.e. for a particular receptor on the surface of the neuron) due to the presence of a binding moiety inherent to the structure of the native neurotoxin molecule (for example, the binding domain of the heavy chain of a botulinum toxin, i.e. the H.sub.C fragment). Thus, for clarity "targeting moiety" or "neuronal targeting moiety" as used herein means a targeting moiety which provides to a neurotoxin specific or enhanced neuronal binding affinity and which is not a natural or inherent feature of the neurotoxin which has such a targeting moiety. Contrarily, "binding moiety" as used herein means the inherent component or domain of the native neurotoxin which provides neuronal binding affinity.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 12. Document ID: US 6080400 A

L4: Entry 12 of 18

File: USPT

Jun 27, 2000

DOCUMENT-IDENTIFIER: US 6080400 A

TITLE: Compositions for the prevention and treatment of verotoxin-induced disease

Detailed Description Text (42):

Fusion proteins comprising the receptor binding domain (i.e., the B subunit) of botulinal toxins may include amino acid residues located beyond the termini of the domains defined above.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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☐ 13. Document ID: US 6060037 A

L4: Entry 13 of 18

File: USPT

May 9, 2000

DOCUMENT-IDENTIFIER: US 6060037 A

TITLE: Compositions that specifically bind to colorectal cancer cells and methods of using the same

Detailed Description Text (86):

Toxins are useful as active moieties. When a toxin is conjugated to an ST receptor binding moiety, the conjugated composition is specifically delivered to a metastasized colorectal cell by way of the ST receptor binding moiety and the toxin moiety kills the cell. Toxins are generally complex toxic products of various organisms including bacteria, plants, etc. Examples of toxins include but are not limited to: ricin, ricin A chain (ricin toxin), Pseudomonas exotoxin (PE), diphtheria toxin (DT), Clostridium perfringens phospholipase C (PLC), bovine pancreatic ribonuclease (BPR), pokeweed antiviral protein (PAP), abrin, abrin A chain (abrin toxin), cobra venom factor (CVF), gelonin (GEL), saporin (SAP), modeccin, viscumin and volkensin. As discussed above, when protein toxins are employed with ST receptor binding peptides, conjugated compositions may be produced using recombinant DNA techniques. Briefly, a recombinant DNA molecule can be constructed which encodes both the ST receptor ligand and the toxin on a chimeric gene. When the chimeric gene is expressed, a fusion protein is produced which includes an ST receptor binding moiety and an active moiety. Protein toxins are also useful to form conjugated compounds with ST receptor binding peptides through non-peptidyl bonds.

Detailed Description Text (116):

One aspect of the present invention relates to a method of treating individuals suspected of suffering from metastasized colorectal cancer. Such individuals may be treated by administering to the individual a pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is a peptide. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54 and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A. chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent

and a radiostable conjugated compound described in Example 1. The individual being treated may be diagnosed as having metastasized colorectal cancer or may be diagnosed as having localized colorectal cancer and may undergo the treatment proactively in the event that there is some metastasis as yet undetected. The pharmaceutical composition contains a therapeutically effective amount of the conjugated composition. A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	KWIC	Draw Desc
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## □ 14. Document ID: US 6051239 A

L4: Entry 14 of 18

File: USPT

Apr 18, 2000

DOCUMENT-IDENTIFIER: US 6051239 A

TITLE: Compositions and methods for systemic delivery of oral vaccines and therapeutic agents

### Detailed Description Text (3):

The present invention provides a modified botulinum toxin which can be used as an oral delivery vehicle for antigenic peptides including, but not limited to, botulinum toxin and other therapeutic agents to the general circulation. It has now been found that botulinum toxin translocates from the gut to the general circulation by binding to serospecific receptors on the mucosal side of polarized gut cells grown in a monolayer. Bound toxin is actively transported across the cells and delivered intact and unmodified on the serosal side of the monolayers. It has been suggested that auxiliary proteins such as hemagglutinin, which is a component of the non-covalent complex of proteins including the botulinum toxin which is released by Clostridium, may mediate binding and transport of the toxin across the gut wall. However, experiments performed with a recombinant form of the holotoxin now demonstrate that the botulinum toxin itself possesses the binding domain that recognizes receptors on the surface of gut cells. Further, it has now been demonstrated that modifications can be made to the light chain of the toxin to render it nontoxic without altering the capability of the protein to translocate from the gut to the general circulation. Accordingly, for the purposes of the present invention, by "modified botulinum toxin" is meant a botulinum toxin which maintains its capability of translocating from the gut to the general circulation but which is nontoxic. Alterations which will render the botulinum toxin nontoxic include mutations to the amino acid sequence of the light chain and deletion of the light chain or portions thereof. In a preferred embodiment, mutations are made to the zinc binding motif or the substrate binding motif of the light chain. For the purposes of this invention, by "nontoxic" it is meant that exposure of the cholinergic nerve endings to the modified botulinum toxin does not result in blockade of transmitter release in the nerve endings and paralysis. The effects of alterations rendering the botulinum toxin nontoxic on the ability of the toxin to translocate from the gut to the general circulation can be routinely performed in accordance with the teachings provided herein so that one of skill may identify modified botulinum toxins of the present invention. Included within this definition of modified botulinum toxins are botulinum toxins which further comprise a selected antigen for a protein other than botulinum toxin or a therapeutic agent.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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## ☐ 15. Document ID: US 5939070 A

L4: Entry 15 of 18

File: USPT

Aug 17, 1999

DOCUMENT-IDENTIFIER: US 5939070 A

TITLE: Hybrid botulinal neurotoxins

### Brief Summary Text (24):

In a separate embodiment of the method, hybrid genes contain the translocation domain of the heavy chain from one serotype, receptor binding domain of the heavy chain from another serotype, combined with the light chain of a third *C. botulinum* serotype. Thus, it is possible to construct a variety of new toxin molecules by combining any of the three functional domains from any *C. botulinum* neurotoxin serotypes.

### Detailed Description Text (16):

In one embodiment, one may manipulate the neurotoxin gene sequences to combine functional domains from different serotypes in a novel gene. For example, the gene segment coding the catalytic light chain of a type A neurotoxin, the gene segment coding the channel forming domain of a type B neurotoxin and the gene segment coding the receptor-binding domain of a type E neurotoxin may be joined together by genetic engineering techniques, and hybrid neurotoxin expressed in the recombinant microorganism.

### Detailed Description Text (47):

Using recombinant DNA technology, it is also possible to construct hybrid toxins containing not only the light chain from one *C. botulinum* serotype and the heavy chain from another, but also hybrid genes which contain the translocation domain of the heavy chain from one serotype, receptor binding domain of the heavy chain from another serotype, combined with the light chain of a third *C. botulinum* serotype. Thus, it is possible to construct a variety of new toxin molecules by combining any of the three functional domains from any *C. botulinum* neurotoxin serotypes.

### Detailed Description Text (51):

Several laboratories have cloned different clostridial neurotoxins genes or gene domains. *C. tetanus* neurotoxin (TeNT) receptor binding domain (about 1.4 kbp) has been expressed in *E. coli* (Fairweather, N. F., et al., *J. Bacteriol.* 165:21-27, 1986; Fairweather, N. F., et al., *FEBS Lett.* 323:218-222, 1993; Makoff, A. J., et al., *Biotechnology* 7:1043-1046, 1989a; Figueiredo, D., et al., *Inf. Immun.* 63:3218-3221, 1995), *Saccharomyces cerevisiae* (Romanos, M. A., et al., *Nucl. Acids Res.* 19:1461-1467, 1991) *Pichia pastoris* (Clare, J. J., et al., *Biotechnology* 7:455-460, 1991) *Lactococcus lactis* (Wells, J. M., et al., *Mol. Microbiol.* 8:1156-1162, 1993) and a baculovirus system (Charles, I. G., et al., *Inf. Immun.* 59:1627-1632, 1991). BoNT/A receptor binding domain (about 1.3 kbp) has been expressed in *E. coli* as well (Clayton, M. C., et al., *Inf. Immunol.* 63:2738-2742, 1995; Middlebrook, J. L. and Brown, J. E., *Curr. Top. Microbiol. Immun.* 195:89-122, 1995).

### Detailed Description Text (63):

The subfragments of the BoNT/A gene encoding the entire light chain (nucleotides 1-1344), the entire heavy chain (nucleotides 1345-3891), channel forming (nucleotides 1345-2687) and receptor binding (nucleotides 2581-3891) domains or their truncated fragments (nucleotides 1345-1789; 1345-2083; 1345-2416; 3301-3891) of the heavy chain were cloned. This was accomplished via the polymerase chain reaction using specific oligonucleotides and of *C. botulinum* chromosomal DNA as a template.

#### CLAIMS:

5. A hybrid botulinal neurotoxin comprising light and heavy chains, which comprise botulinal neurotoxin catalytic, channel forming and receptor binding functional domains, wherein at least two functional domains are from botulinal neurotoxins of different serotypes and wherein the light and heavy chains are linked by a heterobifunctional thiol/amine linker and wherein the specific toxicity of the neurotoxin is at least 10<sup>sup.6</sup> LD<sub>sub.50</sub> /mg protein in vivo.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments
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## ☐ 16. Document ID: US 5879656 A

L4: Entry 16 of 18

File: USPT

Mar 9, 1999

DOCUMENT-IDENTIFIER: US 5879656 A

TITLE: Methods of treating metastatic colorectal cancer with ST receptor binding compounds

#### Detailed Description Text (81):

Toxins are useful as active moieties. When a toxin is conjugated to an ST receptor binding moiety, the conjugated composition is specifically delivered to a metastasized colorectal cell by way of the ST receptor binding moiety and the toxin moiety kills the cell. Toxins are generally complex toxic products of various organisms including bacteria, plants, etc. Examples of toxins include but are not limited to: ricin, ricin A chain (ricin toxin), *Pseudomonas* exotoxin (PE), diphtheria toxin (DT), *Clostridium* perfringens phospholipase C (PLC), bovine pancreatic ribonuclease (BPR), pokeweed antiviral protein (PAP), abrin, abrin A chain (abrin toxin), cobra venom factor (CVF), gelonin (GEL), saporin (SAP), modeccin, viscumin and volkensin. As discussed above, when protein toxins are employed with ST receptor binding peptides, conjugated compositions may be produced using recombinant DNA techniques. Briefly, a recombinant DNA molecule can be constructed which encodes both the ST receptor ligand and the toxin on a chimeric gene. When the chimeric gene is expressed, a fusion protein is produced which includes an ST receptor binding moiety and an active moiety. Protein toxins are also useful to form conjugated compounds with ST receptor binding peptides through non-peptidyl bonds.

#### Detailed Description Text (110):

One aspect of the present invention relates to a method of treating individuals suspected of suffering from metastasized colorectal cancer. Such individuals may be treated by administering to the individual a

pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is a peptide. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-56 and fragments and derivatives thereof. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54 and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a radiostable conjugated compound described in Example 1. The individual being treated may be diagnosed as having metastasized colorectal cancer or may be diagnosed as having localized colorectal cancer and may undergo the treatment proactively in the event that there is some metastasis as yet undetected. The

pharmaceutical composition contains a therapeutically effective amount of the conjugated composition. A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual.

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## ☐ 17. Document ID: US 5695956 A

L4: Entry 17 of 18

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695956 A

TITLE: Clostridium perfringens type a enterotoxin toxoid and methods of preparation and use as a vaccine and therapeutic agent

### Detailed Description Text (2):

The present invention has met the hereinbefore described need. The present invention provides a recombinant DNA plasmid or bacteriophage transfer vector having an Escherichia coli expression vector and a DNA sequence encoding for a Clostridium perfringens type A enterotoxin gene fragment that produces a Clostridium perfringens type A enterotoxin receptor binding domain. The present invention provides a toxoid produced by a recombinant plasmid in an Escherichia coli strain. This plasmid contains a Clostridium perfringens type A enterotoxin gene fragment encoding amino acids 171 through 319 that constitutes the toxoid. This plasmid contains the Escherichia coli expression vector regulatory regions and the Clostridium perfringens type A enterotoxin gene fragment and is capable of producing a toxoid. This plasmid is designated pPH300. The toxoid of this invention recognizes, irreversibly binds to and saturates receptor sites on intestinal membranes and thus effectually competes for those sites with Clostridium perfringens type A enterotoxin. The toxoid of this invention is nontoxic to mammalian cells. This toxoid may be used as a vaccine for preventing the symptoms associated with food poisoning in patients due to Clostridium perfringens type A enterotoxin. The toxoid of this invention may be used to provide a treatment for the symptoms associated with food poisoning in patients due to Clostridium perfringens type A enterotoxin.

### Detailed Description Text (14):

It is a further object of this invention to demonstrate that the 30 carboxy-terminal terminal amino acids of Clostridium perfringens type A enterotoxin are sufficient for recognizing and irreversibly binding to the Clostridium perfringens type A enterotoxin receptor, and thus define these 30 carboxy-terminal amino acids as a functional receptor-binding domain.

### Detailed Description Text (25):

When the .lambda.gtII library of Clostridium perfringens DNA was screened with anti-Clostridium perfringens type A enterotoxin MAb3C9, one positive-scoring plaque was obtained and named lambda ph161 (.lambda.ph161). The construction of the .lambda.gtII library and the resultant .lambda.ph161 is set forth in FIG. 1. Since it is known that MAb3C9 recognizes an epitope which appears to be at or near the receptor-binding domain of Clostridium perfringens type A enterotoxin, this suggests that the positive scoring plaque .lambda.ph161



contains a Clostridium perfringens type A enterotoxin gene insert that encodes a Clostridium perfringens type A enterotoxin receptor-binding domain. Lambda ph161 was isolated and used to generate a temperature sensitive (t.sup.s) lysogen in Escherichia coli Y1089 for phage storage.

Other Reference Publication (1):

"The 31 C-Term Amino Acids of Clostridium perfringens Enterotoxin Defines e Receptor Binding Domain", poster displayed at Annual Meeting of American Society for Microbiology, Anaheim, California (May 1990), P. C. Hanna and B. A. McClane Abstract.

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☐ 18. Document ID: US 5518888 A

L4: Entry 18 of 18

File: USPT

May 21, 1996

DOCUMENT-IDENTIFIER: US 5518888 A

TITLE: ST receptor binding compounds and methods of using the same

Brief Summary Text (97):

Toxins are useful as active moieties. When a toxin is conjugated to an ST receptor binding moiety, the conjugated composition is specifically delivered to a metastasized colorectal cell by way of the ST receptor binding moiety and the toxin moiety kills the cell. Toxins are generally complex toxic products of various organisms including bacteria, plants, etc. Examples of toxins include but are not limited to: ricin, ricin A chain (ricin toxin), Pseudomonas exotoxin (PE), diphtheria toxin (DT), Clostridium perfringens phospholipase C (PLC), bovine pancreatic ribonuclease (BPR), pokeweed antiviral protein (PAP), abrin, abrin A chain (abrin toxin), cobra venom factor (CVF), gelonin (GEL), saporin (SAP), modeccin, viscumin and volkensin. As discussed above, when protein toxins are employed with ST receptor binding peptides, conjugated compositions may be produced using recombinant DNA techniques. Briefly, a recombinant DNA molecule can be constructed which encodes both the ST receptor ligand and the toxin on a chimeric gene. When the chimeric gene is expressed, a fusion protein is produced which includes an ST receptor binding moiety and an active moiety. Protein toxins are also useful to form conjugated compounds with ST receptor binding peptides through non-peptidyl bonds.

Brief Summary Text (126):

One aspect of the present invention relates to a method of treating individuals suspected of suffering from metastasized colorectal cancer. Such individuals may be treated by administering to the individual a pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is a peptide. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that

comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-4 fluorouracil, melphalan, chlorambucil, cis-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, Pseudomonas exotoxin, diphtheria toxin, Clostridium perfringens phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54 and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, cis-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, Pseudomonas exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a radiostable conjugated compound described in Example 1. The individual being treated may be diagnosed as having metastasized colorectal cancer or may be diagnosed as having localized colorectal cancer and may undergo the treatment proactively in the event that there is some metastasis as yet undetected. The pharmaceutical composition contains a therapeutically effective amount of the conjugated composition. A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual.

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L10: Entry 52 of 105

File: USPT

May 16, 2000

US-PAT-NO: 6063768

DOCUMENT-IDENTIFIER: US 6063768 A

TITLE: Application of botulinum toxin to the management of neurogenic inflammatory disorders

DATE-ISSUED: May 16, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
First; Eric R.	South Boston	MA	02127	

US-CL-CURRENT: 514/14; 424/282.1, 424/810, 435/842, 514/2, 514/825, 514/885

## CLAIMS:

I claim:

1. A method for treating neurogenic inflammation comprising, administering a therapeutically effective amount of Clostridium botulinum toxin to antagonize the action of at least one neurogenic inflammatory mediator, whereby said toxin interrupts a neurogenic pathway associated with said neurogenic inflammation.
2. The method of claim 1, wherein the botulinum toxin is selected from the group consisting of botulinum toxin A, B, C, D, E, F and G.
3. The method of claim 1, further comprising treating the neurogenic inflammation by inhibiting at least one neurogenic inflammatory mediator selected from the group consisting of substance-P (SP), calcitonin gene-related peptide (cGRP), vasoactive intestinal peptide (VIP), interleukin-1 (IL-1), interleukin-2 (IL-2), nitric oxide (NO), 5-hydroxytryptamine (5-HT), tumor necrosis factor (TNF), and nerve growth factor (NGF).
4. The method of claim 1, wherein the botulinum toxin is less than about, or equal to 1000 U.
5. The method of claim 1, wherein the neurogenic inflammation is caused by rheumatoid arthritis.
6. The method of claim 1, wherein the neurogenic inflammation is caused by gout.

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MedlineID: 83085378 PubMedID: 6294275

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Nucleotide sequence of the gene coding for Clostridium botulinum (Clostridium argentinense) type G  
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Campbell K, Collins MD, East AK.

Department of Microbiology, Institute of Food Research, Reading Laboratory, Earley G

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Cloning of a Clostridium botulinum type B toxin gene fragment encoding the N-terminus of the heavy chain.

Jung HH, Rhee SD, Yang KH.

Department of Life Science, Korea Advanced Institute of Science and Technology, Taejon, Korea.

*Ginny Portner*  
CM1, Art Unit 1645  
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Mail box 7e12  
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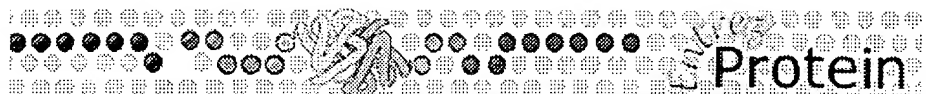
Articles, Links

Nucleotide sequence of the gene coding for Clostridium barati type F neurotoxin: comparison with other clostridial neurotoxins.

Thompson DE, Hutson RA, East AK, Allaway D, Collins MD, Richardson PT.

Department of Microbiology, AFRC Institute of Food Research, Reading Laboratory, UK.

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## ☐ 1: A48940. bontoxilysin (EC ...[gi:477374]

Links

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DEFINITION bontoxilysin (EC 3.4.24.69) B precursor - Clostridium botulinum.  
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VERSION A48940 GI:477374  
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; genetic: #gene bont/b

; superfamily: tetanus toxin

; PIR dates: 19-Dec-1993 #sequence\_revision 18-Nov-1994 #text\_change 18-Jun-1999

KEYWORDS hydrolase; metalloproteinase; neurotoxin; transmembrane protein; zinc.

SOURCE Clostridium botulinum

ORGANISM Clostridium botulinum

Bacteria; Firmicutes; Clostridia; Clostridiales; Clostridiaceae; Clostridium.

REFERENCE 1 (residues 1 to 1291)

AUTHORS Schmidt, J.J., Sathyamoorthy, V. and DasGupta, B.R.

TITLE Partial amino acid sequences of botulinum neurotoxins types B and E

JOURNAL Arch. Biochem. Biophys. 238 (2), 544-548 (1985)

MEDLINE 85197963

PUBMED 3888113

REFERENCE 2 (residues 1 to 1291)

AUTHORS Dasgupta, B.R. and Datta, A.

TITLE Botulinum neurotoxin type B (strain 657): partial sequence and similarity with tetanus toxin

JOURNAL Biochimie 70 (6), 811-817 (1988)

MEDLINE 89000987

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REFERENCE 3 (residues 1 to 1291)

AUTHORS Kurazono, H., Mochida, S., Binz, T., Eisel, U., Quanz, M.,

Grebenstein, O., Wernars, K., Poulain, B., Tauc, L. and Niemann, H.

TITLE Minimal essential domains specifying toxicity of the light chains of tetanus toxin and botulinum neurotoxin type A

JOURNAL J. Biol. Chem. 267 (21), 14721-14729 (1992)

MEDLINE 92340509

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REFERENCE 4 (residues 1 to 1291)

AUTHORS Whelan, S.M., Elmore, M.J., Bodsworth, N.J., Brehm, J.K., Atkinson, T. and Minton, N.P.

TITLE Molecular cloning of the Clostridium botulinum structural gene

encoding the type B neurotoxin and determination of its entire nucleotide sequence

JOURNAL Appl. Environ. Microbiol. 58 (8), 2345-2354 (1992)

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PUBMED 1514783

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AUTHORS Schiavo,G., Benfenati,F., Poulain,B., Rossetto,O., Polverino de Laureto,P., DasGupta,B.R. and Montecucco,C.

TITLE Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin

JOURNAL Nature 359 (6398), 832-835 (1992)

MEDLINE 93063293

PUBMED 1331807

REMARK annotation

REFERENCE 6 (residues 1 to 1291)

AUTHORS Campbell,K.D., Collins,M.D. and East,A.K.

TITLE Gene probes for identification of the botulinal neurotoxin gene and specific identification of neurotoxin types B, E, and F

JOURNAL J. Clin. Microbiol. 31 (9), 2255-2262 (1993)

MEDLINE 94013372

PUBMED 8408542

REFERENCE 7 (residues 1 to 1291)

AUTHORS Szabo,E.A., Pemberton,J.M. and Desmarchelier,P.M.

TITLE Direct Submission

JOURNAL Submitted (~APR-1992) to the EMBL Data Library

COMMENT Botulinum neurotoxins inhibit neurotransmitter release from cholinergic synapses. This toxin is activated by cleavage into two chains linked by a disulfide bond.

FEATURES Location/Qualifiers

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Protein 1..1291

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/note="botulinum neurotoxin type B (BoNT/B)"

Region 2..441

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/note="bontoxilysin B light chain"

Site 230

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/note="zinc (His)"

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/site\_type="binding"

/note="zinc (His)"

Region 442..1291

/region\_name="product"

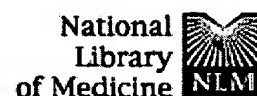
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#### ORIGIN

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Med Dosw Mikrobiol. 1965;17(4):305-11. Polish. No abstract available.  
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PMID: 8534108 [PubMed - indexed for MEDLINE]

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**Nucleotide sequence of the gene coding for non-proteolytic *Clostridium botulinum* type B neurotoxin: comparison with other clostridial neurotoxins.**

Hutson RA, Collins MD, East AK, Thompson DE.

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Department of Microbiology, AFRC Institute of Food Research, Reading Laboratory, UK.

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The neurotoxin gene of non-proteolytic *Clostridium botulinum* type B (strain Eklund 17B) was cloned as a series of overlapping polymerase chain reaction (PCR) fragments generated with primers designed to conserved regions of published botulinal toxin (BoNT) sequences. The 3' end of the gene was obtained by using primers designed to the determined sequence of non-proteolytic BoNT/B and a published downstream region of BoNT/B gene from a proteolytic strain. Translation of the nucleotide sequence derived from cloned PCR fragments demonstrated that the gene encodes a protein of 1291 amino acid residues. Comparative alignment of the derived BoNT/B sequence with those of other published botulinal neurotoxins revealed



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☐ 1: X71343. *C.botulinum* type ...[gi:296148]

[Links](#)

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REFERENCE	1 (bases 1 to 4051)				
AUTHORS	Hutson,R.A., Collins,M.D., East,A.K. and Thompson,D.E.				
TITLE	Nucleotide sequence of the gene coding for non-proteolytic Clostridium botulinum type B neurotoxin: comparison with other clostridial neurotoxins				
JOURNAL	Curr. Microbiol. 28 (2), 101-110 (1994)				
MEDLINE	94122659				
REFERENCE	2 (bases 1 to 4051)				
AUTHORS	Hutson,R.A.				
TITLE	Direct Submission				
JOURNAL	Submitted (06-APR-1993) R.A. Hutson, AFRC Institute of Food Research, Reading Laboratory, Microbiology Dept, Earley Gate, Whiteknights Road, Reading, RG6 2EF, UK				
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# WEST Search History

DATE: Wednesday, October 30, 2002

## Set Name Query

side by side

## Hit Count Set Name

result set

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	L1 same (neurotox\$ or toxin or toxins or endopeptidase or endoproteinase or		
L2	endoprotease or metalloproteinase or metalloprotease or metallopeptidase or clostrid\$ or botulin\$ or botulis\$)	277	L2
L3	L2 same (\$type near b)	0	L3
L4	L2 same (\$type near5 b)	8	L4

END OF SEARCH HISTORY

# WEST Search History

DATE: Wednesday, October 30, 2002

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side by side			result set
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L2	L1 and clostrid\$	16	L2
L3	L1 and botuli\$	12	L3
L4	(L3 or l2) and (coding or nucleic or nucleotide or dna or cdna or mrna or rna or genetic or chromosome or chromosomal or sequence or recombinant)	18	L4
L5	(4683195  4683202  4965188)! [pn]	3	L5
L6	(clostrid\$ or botuli\$ or neurotox\$ or bontoxylylsin\$ or \$endopeptidases or \$metalloproteinases or binary).ti,ab,clm.	33495	L6
L7	L6 and (heavy near5 chain)	89	L7
L8	L6 and ( domain or carbox\$)	3091	L8
L9	L6 and ( domain or domains or carboxy\$ or cterminal or c-terminal)	3125	L9
L10	L9 and (botx or botox or bnx or bottox or bot or serotype or sero-type of botulinum or botulism or btx or bont\$)	105	L10

END OF SEARCH HISTORY

A48940. bontoxilysin (EC ...[gi:477374]

### Links

LOCUS A48940 1291 aa linear BCT 18-JUN-1999  
DEFINITION bontoxilysin (EC 3.4.24.69) B precursor - Clostridium botulinum.  
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18-Jun-1999

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zinc.

SOURCE Clostridium botulinum  
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Bacteria; Firmicutes; Clostridia; Clostridiales; Clostridiaceae;  
Clostridium.

REFERENCE 1 (residues 1 to 1291)  
AUTHORS Schmidt,J.J., Sathyamoorthy,V. and DasGupta,B.R.  
TITLE Partial amino acid sequences of botulinum neurotoxins types B and E  
JOURNAL Arch. Biochem. Biophys. 238 (2), 544-548 (1985)  
MEDLINE 85197963  
PUBMED 3888113

REFERENCE 2 (residues 1 to 1291)  
AUTHORS Dasgupta,B.R. and Datta,A.  
TITLE Botulinum neurotoxin type B (strain 657): partial sequence and  
similarity with tetanus toxin  
JOURNAL Biochimie 70 (6), 811-817 (1988)  
MEDLINE 89000987  
PUBMED 3139097

REFERENCE 3 (residues 1 to 1291)  
AUTHORS Kurazono,H., Mochida,S., Binz,T., Eisel,U., Quanz,M.,  
Greibenstein,O., Wernars,K., Poulain,B., Tauc,L. and Niemann,H.  
TITLE Minimal essential domains specifying toxicity of the light chains  
of tetanus toxin and botulinum neurotoxin type A  
JOURNAL J. Biol. Chem. 267 (21), 14721-14729 (1992)



PUBMED 1634516

**AUTHORS** Whelan,S.M., Elmore,M.J., Bodsworth,N.J., Brehm,J.K., Atkinson,T.  
and Minton,N.P.

JOURNAL Appl. Environ. Microbiol. 58 (8), 2345-2354 (1992)

PUBMED 1514783

**AUTHORS** Schiavo,G., Benfenati,F., Poulain,B., Rossetto,O., Polverino de Laureto,P., DasGupta,B.R. and Montecucco,C.

**JOURNAL** Nature 359 (6398), 832-835 (1992)

PUBMED 1331807

REFERENCE 6 (residues 1 to 1291)

**TITLE** Gene probes for identification of the botulinal neurotoxin gene and specific identification of neurotoxin types B, E, and F

MEDLINE 94013372

PUBMED 8408542

**AUTHORS** Szabo, E.A., Pemberton, J.M. and Desmarchelier, P.M.

JOURNAL Submitted (~APR-1992) to the EMBL Data Library

**COMMENT** Botulinum neurotoxins inhibit neurotransmitter release from cholinergic synapses. This toxin is activated by cleavage into two chains linked by a disulfide bond.

FEATURES	Location/Qualifiers
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Revised: July 5, 2002.

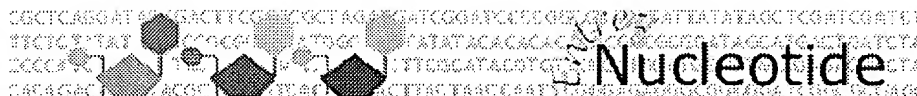
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DATE: Wednesday, October 30, 2002

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L2	receptor near5 binding near5 (moiety or portion)	1345	L2
L3	L2 or l1	3232	L3
L4	L3 same (clostrid\$ or botul\$ or neurotox\$)	18	L4
L5	(h-c or h-chain or hchain or (h near2 c)) and (clostrid\$ or botul\$ or neurotox\$)	2166	L5
L6	(h-c or h-chain or hchain or (h near2 c)) same (clostrid\$ or botul\$ or neurotox\$)	86	L6
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L8	L7 same (type near b)	14	L8
L9	L8 and clostrid\$	0	L9
L10	L8 and neurotoxin	0	L10
L11	L8 and botulinum	0	L11
L12	L7 same clostrid\$	10	L12
L13	hc near5 (fragment or moiety or portion or domain)	520	L13
L14	L13 same (botulinum or botulism or neurotoxin or neuro-toxin or clostrid\$)	3	L14
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L16 L15 not l13 198 L16  
L17 L16 same (clostrid\$ or botul\$ or neurotox\$) 5 L17

END OF SEARCH HISTORY



Display default  Save Text Add to Clipboard Get Subsequence

## Links

10/30/02 8:37 AM

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misc feature

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/note="potential terminator; putative"

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Oct 21 2002 11:56:56

**WEST**

Generate Collection

Print

L12: Entry 2 of 10

File: USPT

Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6461617 B1

TITLE: Recombinant toxin fragments

Abstract Text (1):

A polypeptide has first and second domains which enable the polypeptide to be translocated into a target cell or which increase the solubility of the polypeptide, or both, and further enable the polypeptide to cleave one or more vesicle or plasma-membrane associated proteins essential to exocytosis. The polypeptide thus combines useful properties of a clostridial toxin, such as a botulinum or tetanus toxin, without the toxicity associated with the natural molecule. The polypeptide can also contain a third domain that targets it to a specific cell, rendering the polypeptide useful in inhibition of exocytosis in target cells. Fusion proteins comprising the polypeptide, nucleic acids encoding the polypeptide and methods of making the polypeptide are also provided. Controlled activation of the polypeptide is possible and the polypeptide can be incorporated into vaccines and toxin assays.

Brief Summary Text (9):

(B) Clostridial Neurotoxin Heavy Chain H.sub.N Domain: a portion of the heavy chain which enables translocation of that portion of the neurotoxin molecule such that a functional expression of light chain activity occurs within a target cell. the domain responsible for translocation of the endopeptidase activity, following binding of neurotoxin to its specific cell surface receptor via the binding domain, into the target cell. the domain responsible for formation of ion-permeable pores in lipid membranes under conditions of low pH. the domain responsible for increasing the solubility of the entire polypeptide compared to the solubility of light chain alone.



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L14: Entry 2 of 3

File: USPT

Sep 3, 2002

DOCUMENT-IDENTIFIER: US 6444209 B1

TITLE: Hybrid botulinal neurotoxins

Brief Summary Text (12):

The biologically active neurotoxin of C. botulinum is a dichain molecule of ca. 150 kD in molecular weight. The molecule is composed of two 10 fragments or chains that are termed the heavy chain (Hc, ca. 100 kD) and the light chain (Lc, ca. 50 kD) that are covalently connected by one disulfide bond (FIG. 1). The neurotoxin is synthesized by the organism as a single polypeptide called the protoxin and undergoes post-translational processing termed nicking to generate the two separate chains by at least one protease (Yokosawa, N., et al., J. Gen. Microbiol. 132:1981-1988, 1986; Krysinski, E. and Sugiyama, H., Appl. Environ. Microbiol. 41:675-678, 1981). The two chains are covalently bound through a disulfide bridge. The nicking event occurs in the culture fluid for proteolytic C. botulinum and through the activity of an exogenous enzyme such as trypsin in non-proteolytic strains (Yokosawa, N., et al., supra, 1986; DasGupta, B., J. Physiol. (Paris) 84:220-228, 1990; Kozaki, S., et al., FEMS Microbiol. Lett. 27:149-154, 1985).

05728159 88153072 PMID: 2450068

**Establishment of a monoclonal antibody recognizing an antigenic site common to Clostridium botulinum type B, C1, D, and E toxins and tetanus toxin.**

Tsuzuki K; Yokosawa N; Syuto B; Ohishi I; Fujii N ; Kimura K; Oguma K  
Department of Microbiology, Sapporo Medical College, Japan.

Infection and immunity (UNITED STATES) Apr 1988 , 56 (4) p898-902,  
ISSN 0019-9567 Journal Code: 0246127

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

The partial amino acid sequence of the light-chain (Lc) component of Clostridium botulinum type C1 toxin was determined. The sequence was quite similar to those of the other types of botulinum and tetanus toxins. Nine monoclonal antibodies against botulinum type E toxin were established by immunizing BALB/c mice with type E toxoid or its Lc component. Six antibodies reacted with the heavy-chain component and three reacted with the Lc component of the toxin. One of the latter three antibodies reacted with botulinum type B, C1, and D toxins and tetanus toxin, as well as botulinum type E toxin. This antibody recognized the Lc components of these toxins, indicating that there exists one common antigenic determinant on the Lc regions of these toxins.

Tags: Comparative Study; Support, Non-U.S. Gov't

Descriptors: \*Antibodies, Monoclonal--immunology--IM; \*Bacterial Toxins--immunology--IM; \*Botulinum Toxins--immunology--IM; \*Clostridium botulinum--immunology--IM; \*Tetanus Toxin--immunology--IM; Amino Acid Sequence; Clostridium perfringens--immunology--IM; Epitopes; Immunosorbent Techniques; Molecular Sequence Data

CAS Registry No.: 0 (Antibodies, Monoclonal); 0 (Bacterial Toxins); 0 (Botulinum Toxins); 0 (Epitopes); 0 (Tetanus Toxin)

Record Date Created: 19880419

**Characterization of bacteriophage nucleic acids obtained from Clostridium botulinum types C and D.**

Fujii N ; Oguma K ; Yokosawa N; Kimura K; Tsuzuki K

Department of Microbiology, Sapporo Medical College, Japan.

Applied and environmental microbiology (UNITED STATES) Jan 1988 , 54

(1) p69-73, ISSN 0099-2240 Journal Code: 7605801

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

Nontoxigenic strains of Clostridium botulinum types C and D are converted to toxigenic strains by infection with specific Tox+ bacteriophages. The nucleic acids were extracted from five converting phages, c-st, c-468, c-203, c-d6f, and d-1873, and one nonconverting phage, c-n71, and treated with nucleases. The nucleic acids isolated were not digested by RNase A, but were digested by DNase I and exonuclease III, indicating that they were double-stranded DNA. On the basis of the restriction endonuclease digestion patterns on 0.8% agarose gel electrophoresis, the length of c-st, c-n71, c-468, and c-d6f phage DNAs was estimated to be about 110 kilobase pairs and that of c-203 and d-1873 was about 150 kilobase pairs. The digestion patterns of c-st, c-468, and c-n71 phage DNAs by PstI and HindIII were very similar. High homology was observed in the dot hybridization test. For other phages and nucleases, a good similarity was not observed. Only a little similarity was observed between c-203 and c-d6f phages. The existence of the structural genes for the toxin in both c-st and c-n71 phages was confirmed by the hybridization test with these phage DNAs and the oligonucleotide probe which represented the DNA sequence predicted for the N-terminal amino acids (2 to 17) of C. botulinum type C toxin. The loss of the converting ability of c-n71 phage may be caused not by the deletion of the tox+ gene but rather by the base mutation in c-st phage DNA.

Tags: Support, Non-U.S. Gov't

Descriptors: \*Bacteriophages--genetics--GE; \*Clostridium botulinum --genetics--GE; \*DNA, Viral--analysis--AN; Amino Acid Sequence; Botulinum Toxins--analysis--AN; Botulinum Toxins--genetics--GE; Molecular Sequence Data; Molecular Weight; Nucleic Acid Hybridization

CAS Registry No.: 0 (Botulinum Toxins); 0 (DNA, Viral)

Record Date Created: 19880404


?logoff hold

## 11 Functional Domains of Botulinal Neurotoxin.

12 Binding to cell surface. The carboxyl terminus of botulinal heavy chain is responsible for receptor binding on the cell surface. Initial work done using tetanus toxin, which is very similar in structure to botulinum neurotoxin, showed binding to cell receptors involved a multiple step binding sequence. The ten C-terminal amino acids are essential for initial receptor recognition on the motor neuron via a low affinity binding site while a sequence in the middle of the heavy chain was responsible for higher affinity secondary binding through a different protein receptor (Halpern, J. and Loftus, A., J. Biol. Chem. 268:11188-11192, 1993).

13 Evidence shows that binding by type B botulinum neurotoxin occurs in a similar fashion (Nishiki, T., et al., J. Biol. Chem. 269:10498-10503, 1994). The binding of type B neurotoxin to synaptosomes has been shown to be related to the presence of sialic acid containing motor neuron membrane components such as gangliosides G.sub.D1a and G.sub.T1b

as well as a partially purified 58 kD protein that has been tentatively determined to be synaptogamin. There is minimal binding of the neurotoxin to the 58 kD high affinity receptor in the absence of the low affinity gangliosides. This indicates that the initial low affinity binding to gangliosides which are prevalent on the cell surface by the carboxyl-terminal amino acids is followed by a high affinity binding to the 58 kD protein by an undetermined region that is more amino terminal possibly in the central portion of the heavy chain. Treatment of synaptosomes with proteases and or sialidase decreased binding of the neurotoxin to the synaptosomes.



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**ANALYSIS TOOLS**

## EBI Generic DB Entry Retrieval

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ID      CBBONT      standard; DNA; PRO; 4041 BP.
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AC      M81186;
XX
SV      M81186.1
XX
DT      28-MAY-1992 (Rel. 32, Created)
DT      04-MAR-2000 (Rel. 63, Last updated, Version 4)
XX
DE      Clostridium botulinum neurotoxin type B (botB) gene, complete cds.
XX
KW      botB gene; neurotoxin type B.
XX
OS      Clostridium botulinum
OC      Bacteria; Firmicutes; Clostridia; Clostridiales; Clostridiaceae;
OC      Clostridium.
XX
RN      [1]
RP      1-4041
RA      Whelan S.M., Elmore M.J, Bodsworth N.J., Brehm J.K., Atkinson T.,
RA      Minton N.P.;
RT      "Complete nucleotide sequence of the Clostridium botulinum gene encoding
RT      the type B neurotoxin";
RL      Unpublished.
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DR      SWISS-PROT; P10844; BXB_CLOBO.
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# WEST Search History

DATE: Wednesday, October 30, 2002

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side by side			result s t
	<i>DB=USPT; PLUR=YES; OP=AND</i>		
L1	heavy.clm. same chain.clm.	931	L1
L2	L1 and clostrid\$	16	L2
L3	L1 and botuli\$	12	L3
L4	(L3 or l2) and (coding or nucleic or nucleotide or dna or cdna or mrna or rna or genetic or chromosome or chromosomal or sequence or recombinant)	18	L4
L5	(4683195  4683202  4965188)! [pn]	3	L5
L6	(clostrid\$ or botuli\$ or neurotox\$ or bontoxyilysin\$ or \$endopeptidases or \$metalloproteinases or binary).ti,ab,clm.	33495	L6
L7	L6 and (heavy near5 chain)	89	L7
L8	L6 and ( domain or carbox\$)	3091	L8
L9	L6 and ( domain or domains or carboxy\$ or cterminal or c-terminal)	3125	L9
L10	L9 and (botx or botox or bnx or bottox or bot or serotype or sero-type of botulinum or botulism or btx or bont\$)	105	L10
L11	l1 same l6	9	L11
L12	(hchain or h-chain or hc or heavy) same (botulinum or botulism or botx or botox or bnx or bottox or bot or btx or bont or bont\$ or clostrid\$)	289	L12
	L12 same (vector or recombinant or mutation		



L13	or mutant or mutagenesis or dna or gene or genetic or coding or encoding or sequence or nucleic or nucleotide or nuclear or polynucleotide or dna or cdna or mrna or rna)	38	L13
L14	(urine or urina\$ or urinary).ti,ab,clm.	5642	L14
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L16	L15 and (spin or precipit\$ or centrifug\$ or sediment\$)	1641	L16
L17	L16 and (top or supernatant or super-natant or separat\$ or remov\$ or decant\$)	1597	L17
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L25	L24 same (centrifug\$ or spin\$ or precipit\$ or sediment\$)	108	L25
L26	L25 and (tgfb or tgf\$ or tgf-beta or tgfbeta)	17	L26
L27	('5883124'  '5015571')[PN]	2	L27

L28	naoh.clm. and hcl.clm. and (urin\$.clm.	3	L28
L29	centrif\$.clm. and urin\$.clm.	69	L29
L30	L29 and (amicon or amikon or dializ\$ or dialysis)	18	L30

END OF SEARCH HISTORY

ID BXB\_CLOBO\_3; parent: BXB\_CLOBO  
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SQ Sequence 850 AA;  
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↑↑ mm↑↑  
mm

General	<b>Description</b>	References	Comments	Links	Keywords	Features	Sequence
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## General information

Entry name	BXB_CLOBO
Accession number	<u>P10844</u> , <u>P10843</u>
Created	Rel. 11, 1-JUL-1989
Sequence update	Rel. 26, 1-JUL-1993
Annotation update	Rel. 41, 15-JUN-2002

## Description and origin of the Protein

Description	Botulinum neurotoxin type B precursor (EC <u>3.4.24.69</u> ) (BoNT/B) (Bontoxilysin B).
Gene name(s)	BOTB.
Organism source	Clostridium botulinum.
Taxonomy	Bacteria; Firmicutes; Clostridia; Clostridiales; Clostridiaceae Clostridium.
NCBI TaxID	<u>1491</u>

## References

- |     |  |                              |
|-----|--|------------------------------|
| [1] | Whelan,S.M., Elmore,M.J., Bodsworth,N.J., Brehm,J.K.,<br>Atkinson,T., Minton,N.P.,<br><b>Molecular cloning of the Clostridium botulinum structural<br/>gene encoding the type B neurotoxin and determination o<br/>its entire nucleotide sequence.</b><br>(1992) <i>Appl. Environ. Microbiol.</i> <b>58</b> :2345-2354 |                              |
|     | Position   | SEQUENCE FROM N.A.           |
|     | Medline  | <u>92384550</u>              |
|     | PubMed   | <u>1514783</u>               |
| [2] | Szabo,E.A., Pemberton,J.M., Desmarchelier,P.M., Submitted  |                              |
|     | Position   | SEQUENCE OF 35-245 FROM N.A. |
|     | Comments   | STRAIN=NCTC 7273;            |

- [3] Campbell,K., East,A.K., Collins,M.D.,  
**Gene probes for identification of the botulinum neurotoxin gene and specific identification of neurotoxin types B, E and F.**

(1993) *J. Clin. Microbiol.* 31:2255-2262

Position SEQUENCE OF 633-993 FROM N.A.

Comments STRAIN=NCTC 7273;

Medline 94013372

PubMed 8408542

- [4] Dasgupta,B.R., Datta,A.,  
**Botulinum neurotoxin type B (strain 657): partial sequence and similarity with tetanus toxin.**

(1988) *Biochimie* 70:811-817

Position SEQUENCE OF 1-44 AND 441-466.

Comments STRAIN=657;

Medline 89000987

PubMed 3139097

- [5] Schmidt,J.J., Sathyamoorthy,V., Dasgupta,B.R.,  
**Partial amino acid sequences of botulinum neurotoxins types B and E.**

(1985) *Arch. Biochem. Biophys.* 238:544-548

Position SEQUENCE OF 1-16 AND 441-458.

Comments STRAIN=OKRA;

Medline 85197963

PubMed 3888113

- [6] Schiavo,G., Rossetto,O., Santucci,A., Dasgupta,B.R.,  
Montecucco,C.,  
**Botulinum neurotoxins are zinc proteins.**

(1992) *J. Biol. Chem.* 267:23479-23483

Position IDENTIFICATION AS ZINC-PROTEASE

	Medline	<u>93054694</u>
	PubMed	<u>1429690</u>
[7]	Schiavo,G., Benfenati,F., Poulain,B., Rossetto,O., de Laureto,P.P., Dasgupta,B.R., Montecucco,C., <b>Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin.</b> (1992) <i>Nature</i> 359:832-835	
	Position	IDENTIFICATION OF SUBSTRATE.
	Medline	<u>93063293</u>
	PubMed	<u>1331807</u>

### Comments

#### FUNCTION

BOTULINUS TOXIN ACTS BY INHIBITING NEUROTRANSMITTER RELEASE. IT BINDS TO PERIPHERAL NEURONAL SYNAPSES, IS INTERNALIZED AND MOVES BY RETROGRADE TRANSPORT UP THE AXON INTO THE SPINAL CORD WHERE IT CAN MOVE BETWEEN POSTSYNAPTIC AND PRESYNAPTIC NEURONS. IT INHIBITS NEUROTRANSMITTER RELEASE BY ACTING AS A ZINC ENDOPEPTIDASE THAT CLEAVES THE 76-GLN-|-PHE-77 BOND OF SYNAPTOBREVIN-2.

#### CATALYTIC ACTIVITY

LIMITED HYDROLYSIS OF PROTEINS OF THE NEUROEXOCYTOSIS APPARATUS, SYNAPTOBREVINS, SNAP25 OR SYNTAXIN. NO DETECTED ACTION ON SMALL MOLECULE SUBSTRATES.

COFACTOR	BINDS 1 ZINC ION PER SUBUNIT (BY SIMILARITY).
SUBUNIT	DISULFIDE-LINKED HETERODIMER OF A LIGHT CHAIN (L) AND A HEAVY CHAIN (H). THE LIGHT CHAIN HAS TH PHARMACOLOGICAL ACTIVITY, WHILE THE N-AND C-TERMINAL OF THE HEAVY CHAIN MEDIATE CHANNEL FORMATION AND TOXIN BINDING, RESPECTIVELY.
SUBCELLULAR LOCATION	SECRETED.
MISCELLANEOUS	THERE ARE SEVEN ANTIGENICALLY DISTINCT FORMS OF BOTULINUM NEUROTOXIN: TYPES A, B, C1, D, E, F, AND G.
SIMILARITY	BELONGS TO PEPTIDASE FAMILY M27

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### Database cross-references

EMBL	<u>M81186</u> ;AAA23211.1;-.
	<u>Z11934</u> ;CAA77991.1;-.
	<u>X70817</u> ;CAA50148.1;-.
	S07128;S07128.
	S07155;S07155.

PIR	S08562;S08562. S08573;S08573. S08574;S08574. A48940;A48940.
HSSP	P10845; <u>3BTA</u> .
MEROPS	<u>M27.002</u> ;.-.
InterPro	<u>IPR000395</u> ;Bontoxilysin. <u>IPR000130</u> ;Zn_MTpeptdse.
Pfam	<u>PF01742</u> ;Peptidase_M27;1.
PRINTS	<u>PR00760</u> ;BONTOXILYSIN.
ProDom	<u>PD001963</u> ;Bontoxilysin;1.
PROSITE	<u>PS00142</u> ;ZINC_PROTEASE;1.

### Keywords

Neurotoxin; Transmembrane; Hydrolase; Metalloprotease; Zinc;

### Features

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Key	Begin	End	Length	Description
<u>INIT MET</u>	0	0	1	
<u>CHAIN</u>	1	440	440	BOTULINUM NEUROTOXIN B, LIGHT-CHAIN.
<u>CHAIN</u>	441	1290	850	BOTULINUM NEUROTOXIN B, HEAVY-CHAIN.
<u>METAL</u>	229	229	1	ZINC (CATALYTIC) (BY SIMILARITY).
<u>ACT SITE</u>	230	230	1	BY SIMILARITY.
<u>METAL</u>	233	233	1	ZINC (CATALYTIC) (BY SIMILARITY).
<u>DISULFID</u>	436	445	10	INTERCHAIN (PROBABLE).
<u>CONFLICT</u>	29	29	1	T -> M (IN REF. 4).
<u>CONFLICT</u>	217	217	1	R -> G (IN REF. 2).
<u>CONFLICT</u>	224	224	1	A -> S (IN REF. 2).
<u>CONFLICT</u>	463	463	1	S -> R (IN REF. 4).

10/31/02  
10/02  
Searches  
BP

### Sequence information

Length: 1290 aa, molecular weight: 150670 Da, CRC64 checksum:  
D21746E2C024DF43

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PVTINNFNYN DPIDNNNIIM MEPPFARGTG RYYKAFKITD RIWIIPERYT FGYPEDFNK      60
SSGIFNRDVC EYYDPDYLNT NDKKNIFLQT MIKLFNRIKS KPLGEKLLEM IINGIPYLGD      120
RRVPLEEFNT NIASVTVNKL ISNPGEVERK KGIFANLIIF GPGPVLNENE TIDIGIQNHF      180
ASREGFGGIM QMKFCPEYVS VFNNVQENKG ASIFNRRGYF SDPALILMHE LIHVLHGLYG      240
IKVDDLPIPV NEKKFFMQST DAIQAEELYT FGGQDPSIIT PSTDKSIYDK VLQNFGRIVD      300
RLNKVLVCIS DPNININIKY NKFKDKYKFV EDSEGKYSID VESFDKLYKS LMFQFTETNI      360
AENYKIKTRA SYFSDSLPPV KIKNLLDNEI YTIIEGFNIS DKDMEKEYRG QNKAINKQAY      420
EEISKEHLAV YKIQMCKSVK APGICIDVDN EDLFFIADKN SFSDDLKNE RIEYNTQSNY      480
IENDFPINEL ILDTDLISKI ELPSENTESL TDFNVDPVYV EKQPAIKKIF TDENTIFQYL      540
YSQTFPLDIR DISLTSSFDD ALLFSNKVYS FFSMDYIKTA NKVVEAGLFA GWVKQIVNDF      600
VIEANKSNTM DKIAISLIV PYIGLALNVG NETAKGNFEN AFEIAGASIL LEFIPELLIP      660
VVGAFLLSEY IDNKNKIIKT IDNALTNRNE KWSMDYGLIV AQWLSTVNTQ FYTIKEGMYK      720
ALNYQAQALE EIIKYRYNIY SEKEKSNINI DFNDINSKLN EGINQAIDNI NNFINGCSVS      780
YLMKKMIPLA VEKLLDFDNT LKKNLLNYID ENKLYLIGSA EYEKSKVNKY LKTIMPFDSL      840
IYTNDTILIE MFNKNYSEIL NNIILNLRYK DNNLIDLSGY GAKVEVYDGV ELNDKNQFKL      900
TSSANSKIRV TQNQNIIFNS VFLDFSVSFW IRIPKYKNDG IQNYIHNEYT IINCMKNNSG      960
WKISIRGNRI IWTLIDINGK TKSVPFEYNI REDISEYINR WFFVTITNNL NNAKIYINGK      1020
LESNTDIKDI REVIANGEII FKLDGDIDRT QFIWMKYFSI FNTELSQSN I EERYKIQSYS      1080
EYLKDFWGNP LMYNKEYYMF NAGNKNYSYK LKKDSPVGEI LTRSKYNQNS KYINYRDLVI      1140
GEKFIIIRKS NSQSINDDIV RKEDYIYLD FNLNQEWVRY TYKYFKKEEE KLFLAPISDS      1200
DEFYNTIQIK EYDEQPTYSC QLLFKKDEES TDEIGLIGIH RFYESGIVFE EYKDYFCISK      1260
WYLKEVKRKP YNLKLGNCWQ FIPKDEGWTE                                     1290

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General	Description	References	Comments	Links	Keywords	Features	Sequence
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